Botulinum Toxin Treatment in Parkinson's Disease and Atypical Parkinsonian Disorders

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Introduction

Therapeutic applications of botulinum toxin (BoNT) have continued to expand into many clinical fields, since its first therapeutic use in the 1970s for strabismus [1]. BoNT was initially approved by the United States Food and Drug Administration (FDA) in 1989 for the treatment of strabismus, blepharospasm, and other facial spasms including hemifacial spasm. The number and scope of therapeutic and non-therapeutic (cosmetic) applications of BoNT is not matched by any other treatments [2, 3]. Besides cosmetic uses, chiefly in the treatment of wrinkles, BoNT has become the standard of care for the management of conditions like focal dystonia (e.g., blepharospasm, cervical dystonia, oromandibular dystonia, writer's cramp), spasticity, hyperhidrosis, hemifacial spasm, and a variety of ophthalmological and otolaryngeal disorders. It is also increasingly used for various gastroenterological and urological indications and as an analgesic therapy including migraines. In this chapter, we will review the role of BoNT in the treatment of multiple symptoms experienced by patients with Parkinson's disease (PD) and atypical parkinsonism (Table 1).

There are five different BoNT available at this time in Europe and America; four contain BoNT serotype A (onabotulinumtoxinA or Botox®, abobotulinumtoxinA or Dysport® and incobotulinumtoxinA or Xeomin®) and the other contains BoNT serotype B (rimabotulinumtoxinB or Myobloc®/NeuroBloc®). There are several other

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Table 1 Botulinum toxin in the treatment of symptoms associated with Parkinson's disease and atypical parkinsonism

Tremor
Freezing of gait
Dystonia
Blepharospasm and lid apraxia
Bruxism
Limb dystonia—upper and lower extremities—striatal hand/foot
Axial dystonia
Camptocormia
Cervical dystonia
Sialorrhea
Hyperhidrosis
Dysphagia (achalasia)
Seborrhea
Overactive bladder
Constipation
Levodopa-related dystonia
Myoclonus
Dystonic clenched fist
Myorhythmia

forms of BoNT used in other parts of the world, e.g., Prosigne or CBTX-A in China and Meditoxin in South Korea, or are still in development, e.g., daxibotulinumtoxinA (RT002). Potency and doses of BoNT vary depending on the form of toxin and it is, therefore, absolutely critical that the treating clinician is aware of the source and pharmacology of the particular product used. The doses given for a particular toxin cannot be readily transferred to doses of other products, even if they are of the same toxin serotype. Hence, in this chapter different brand names will be mentioned as they have different properties and dosages that are unique to them.

Parkinson's Disease and Atypical Parkinsonism

Parkinson's disease (PD) is a common neurodegenerative disorder, affecting about 1% of the population over the age of 60 years. The mean age of onset is 55 years and men are slightly more frequently affected. According to the United Kingdom PD Society Brain Bank, the clinical criteria for probable PD require the presence of bradykinesia and at least one of the following features: rigidity, rest tremor of 4–6 Hz, or postural instability. In addition, flexed posture and freezing (motor blocks) have been included among classic features of parkinsonism, with PD as the most common form [4]. PD patients may have masked faces, low volume speech, dysphagia, sialorrhea, and shuffling gait. In addition to motor features, the patient

Table 2 Level of evidence support treatment of different symptoms associated with PD with BoNT

Disorder	Level of evidence
Overactive bladder [9]	Level A for BoNT serotype A and B
Hyperhidrosis [9]	Level A for BoNT serotype A, Level B for onabotulinumtoxinA and abobotulinumtoxinA individually
	Level U—rimabotulinumtoxinB and incobotulinumtoxinA
Sialorrhea [9]	Level B—onabotulinumtoxinA, abobotulinumtoxinA and rimabotulinumtoxinB
	Level U—incobotulinumtoxinA
Tremor, freezing of gait, camptocormia, constipation, seborrhea	Level U recommendation
Cervical dystonia [10]	Level A—abobotulinumtoxinA and rimabotulinumtoxinB
	Level B—onabotulinumtoxinA and incobotulinumtoxinA
Blepharospasm [10]	Level B—onabotulinumtoxinA, incobotulinumtoxinA
	Level B—abobotulinumtoxinA
	Level U—rimabotulinumtoxinB
Oromandibular dystonia [11]	Level C—onabotulinumtoxinA, abobotulinumtoxinA
	Level U—rimabotulinumtoxinB and incobotulinumtoxinA

Level A: established as effective (requires at least two consistent class I studies)
Level B: probably effective (requires at least one class I study or at least two consistent class II studies)
Level C: possibly effective (requires at least one class II study or two consistent class III studies)
Level U: inadequate or conflicting data, treatment is unproven

may notice multiple non-motor symptoms such as shoulder pain, depression, sleep problems, forgetfulness, and autonomic problems including orthostatic hypotension, constipation, urinary frequency, urgency, and incontinence. It is increasingly evident that PD is a heterogeneous disorder with variable clinical-pathologic phenotypes and natural history [5].

In addition to PD, there are many other parkinsonian disorders, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) that have symptoms which may be amenable to the treatment with BoNT. It is beyond the scope of this review to discuss these atypical parkinsonian disorders but the reader is referred to a recent review article [6].

While levodopa and other dopaminergic and non-dopaminergic drugs are quite effective in controlling the motor and non-motor symptoms of PD and to a lesser degree in atypical parkinsonism, BoNT has emerged as an effective therapeutic option for treatment of many symptoms associated with PD and atypical parkinsonism [6–8] (Table 2). In a retrospective study of 160 patients with idiopathic PD or atypical parkinsonism who received BoNT treatment, the indications for BoNT treatment were pain (50% cases), dystonia (26.2%), sialorrhea (18.7%), camptocormia (1.2%), and freezing of gait (FOG) (0.6%) [12]. Eighty-one percent of all PD

patients reported benefits with BoNT treatment and similar results were seen in atypical parkinsonism group, as well. This review is organized according to the various parkinsonian symptoms and signs treated with BoNT.

Tremor

Rest tremor in hand is one of the common features of PD but postural and kinetic tremor may also be present. Re-emergent tremor, which appears after the hand is held in the postural position for some time, is a more bothersome tremor in PD patients than rest tremor as it often interferes with daily activities like holding a newspaper or a cup [13]. Even though tremor usually responds to conventional anti-PD treatment, other treatments such as BoNT may have to be considered when satisfactory relief is not obtained with conventional therapy and before considering deep brain stimulation (DBS).

Phenomenologically, essential tremor (ET) overlaps with re-emergent tremor in that it is a form of postural tremor [14]. BoNT has been shown to be effective in the treatment of essential tremor (ET) in two well-designed double-blind, placebo-controlled studies [15, 16]. Both these studies used onabotulinumtoxinA and showed reduction in the amplitude of tremor. The main complication in both studies was extensor finger weakness. Both studies used "fixed-dose-fixed muscle" approach rather than individualizing the BoNT dose and muscle selection based on specific needs. As a result, we recommend modified protocol with markedly reduced doses in the forearm extensors or completely eliminating injections in the extensor muscle group. In our center, we have achieved comparable tremor control with this modified technique and less incidence of extensor finger weakness [7, 14, 144].

Some studies have shown benefits of BoNT in other types of tremor including PD-related rest tremor. One open-label study examined the effects of BoNT on disabling tremors, classified as dystonic, essential, combination of dystonic and essential, parkinsonian, peripherally induced and cerebellar-outflow tremor and noted that 67% of 51 patients noticed some improvement in tremors with average duration of benefits lasting for 10.5 weeks [17]. In another open-label study, BoNT was injected into forearm and arm of 26 patients (12 with PD and 14 with ET) [18]. At 6 weeks after injection, 38% of the patients (ten total; five PD and five ET) reported moderate to marked subjective improvement in functional benefits. Only ET patients showed statistically significant improvement when pre- and post-injection scores were compared on the Webster Tremor and Global Disability Scales. In 2 of 12 PD patients (17%) and 3 of 14 ET patients (21%) more than 50% reduction in amplitude, assessed by accelerometry, was found after BoNT injections. An earlier study looking at outcome after BoNT treatment in 187 patients with limb disorders, 2 of 15 patients (13.3%) with PD tremor showed marked subjective improvement and significant decrement in tremor amplitude (more than 50% reduction) using quantitative measures [19]. In a single-blind, placebo-controlled study comparing the effects of 25–50 units of BoNT to placebo at 1 month, 60% of the BoNT group

demonstrated benefits >30% above the placebo group; 40% improvement in postural PD-like tremor and 57% improvement in ET-like tremor, but there was no significant change in the rest tremor [20]. In a small open-label study seven patients with upper limb PD tremor were injected with incobotulinumtoxinA, using clinical and kinematic assessments to determine the dose and distribution of BoNT [21]. The study showed significant improvement across time points, represented by a reduction in the clinical scale score, in UPDRS Item 20 (rest tremor) at 1, 2, 3 months with respect to the baseline ($p = 0.005$, $p = 0.003$, $p = 0.007$, respectively), Item 21 (action and postural tremor) at 3 months ($p = 0.016$), and spiral drawing at 4 months with respect to the baseline ($p = 0.028$). In a subsequent, 38-week, open-label study using kinematic and biomechanics of tremor for deciding injection pattern of incobotulinumtoxinA in 28 PD patient showed statistically significant decrease in mean UPDRS item 20 at week 16 ($p = 0.006$) and at week 32 ($p = 0.014$), and in the Fahn-Tolosa-Marin Tremor Severity (FTMTS) scores at week 6 ($p = 0.024$) [22]. Further studies are needed to establish the efficacy of BoNT in patients with PD-related tremor [23]. Also, the findings from the published studies suggest that treatment protocols need to be individualized based on tremor type; for example, patients with prominent pronation-supination type hand tremor may require injection into biceps muscles in addition to wrist and finger flexors (Jankovic 2009b). Additionally, kinematic technology may be helpful in guiding the injection pattern when it is difficult to visually judge and decompose the motion involved during the tremor [24].

PD patients, in addition to hand or leg tremor, may also have chin, lip, jaw, or tongue tremor [25, 26]. Jaw tremor resulting in vertical or horizontal oscillation of the mandible may be difficult to treat with conventional dopaminergic medications or other anti-PD therapies [8]. In a case series of three patients with PD jaw tremor, injection of abobotulinumtoxinA (mean dose 53 units in each muscle) in both masseters was associated with subjective and clinical improvement [27]. The improvement in tremor was also noted on the video recording taken before and 4–9 weeks after injections. There were no serious side effects. There is also a case report of BoNT injections in bilateral digastric and masseters in reducing position-sensitive (tremor absent at rest but present when jaw partially opened) jaw tremor that worsened with speaking [28].

Freezing of Gait (FOG)

FOG refers to a sudden inability to initiate or continue ongoing gait, especially when starting to walk, making turns or walking through narrow passages with the associated perception that the feet are "stuck to the ground" [4]. In PD, FOG is associated with disease severity, although it can be seen in early stages of PD, as well [29, 30]. However, if FOG is the first presenting sign, atypical forms of parkinsonism, especially progressive supranuclear palsy (PSP), should be suspected [31]. FOG episodes that are less responsive or nonresponsive to dopaminergic treatments

are the greatest therapeutic challenge. Some believe that FOG may be dystonic, associated with disinhibited foot grasp and others believe that it may be mediated by non-dopaminergic mechanisms, including damage to the brainstem pedunculopontine nucleus [29, 32].

Various treatment approaches exist for FOG, including pharmacological agents, surgical options, as well as physiotherapy, including the use of visual cues (e.g., stepping over an obstacle), auditory cues (e.g., musical rhythm), and other sensory techniques [33, 34]. In the treatment of FOG, it is important to distinguish between "on freezing" and "off freezing." "Off freezing," like other PD symptoms can be treated by preventing the patient from going "off." "On freezing" for unclear reasons tends to worsen by increasing the dosage of levodopa. In patients with dopamine-responsive FOG, in addition to dopaminergic medications (levodopa or dopamine agonists), trial of amantadine, rasagiline, selegiline, droxidopa, cholinergic drugs, CNS stimulants, and DBS may also be considered [35–39].

There have been few clinical trials of BoNT for the treatment of FOG. The use of BoNT into the distal leg muscles was based on the theory that involuntary contractions of these muscles may have a role in FOG. These studies involved injection of BoNT serotype A in gastrocnemius and soleus muscles unilaterally or bilaterally [40, 41]. While one of these studies showed marked improvement in 40% of the patients in 6 weeks, these results could not be reproduced in later studies using either BoNT serotype A or B [42–44]. Hence, the use of BoNT for FOG is now used only very rarely [34, 45].

Dystonia

Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both [46]. Dystonic movements are typically patterned (same muscles keep contracting), twisting, and tremulous. Some forms of dystonia, such as blepharospasm and laryngeal dystonia, are not associated with abnormal postures, but are characterized by focal involuntary contractions that interfere with physiological opening or closing of the eyelids or the larynx. About 60% of PD patients with disease onset before age 40 can have different forms of dystonia and 30% of PD patients overall have dystonia [47]. The majority of the cases with dystonia as the presenting PD symptom had involvement of foot, which often can be painful. "Striatal" foot with unilateral equinovarus dystonia posture of the foot with great toe extension, flexion of the remaining toes and extension of the big toe, or "striatal" hand deformity, with flexion at the metacarpophalangeal joint, flexion of distal interphalangeal joints, and ulnar hand deviation may be seen in up to 40% of untreated PD patients with advanced disease [48]. These may be reversible with therapy but if left untreated, will result in fixed deformity. The cause of these deformities is unknown, but may be due to a combination of dystonia, low striatal dopamine, and fibrosis with alterations in soft-tissue plasticity and visco-elasticity [49]. Since levodopa has a variable

effect on these deformities, BoNT has been used to effectively correct the abnormal postures in some patients with striatal hand and striatal foot and toe deformities particularly when not accompanied by fixed contractures [50, 51].

Blepharospasm and Lid Apraxia

Blepharospasm is an involuntary, forceful eye closure, which may be present in some patients with PD, but this form of focal dystonia is more common in patients with atypical parkinsonism. When blepharospasm occurs in the setting of parkinsonism, it is often associated with apraxia of eyelid opening (ALO). Indeed, blepharospasm in combination with ALO should raise the possibility of atypical parkinsonism, such as PSP [52].

The mechanism of ALO is not well understood but it has been thought to represent another form of a focal eyelid dystonia due to abnormal contractions of the pretarsal orbicularis oculi, levator palpebrae inhibition, or eyelid freezing [53].

ALO is often difficult to treat with BoNT and is one of the most common reasons for treatment failures in patients thought to have blepharospasm. There are rare reports of injections into the orbital part of orbicularis oculi that might be helpful [54]. Most reports, however, suggest that pre-tarsal injections of BoNT are usually needed to obtain some benefit in patients with ALO [53]. However, when blepharospasm triggers the ALO, then the conventional treatment with BoNT into pretarsal part of the orbicularis oculi can be very effective in treating both sufficiently to obtain optimum results and there is no need to do additional injections [55]. In addition to significantly higher response rate and longer duration of maximum response, pretarsal injections are associated with lower frequency of major side effects such as ptosis [56]. Avoiding the midline of upper lid, the area where the levator palpebrae muscle is located minimizes the risk of ptosis. Injection into the Riolan's muscle at the medial and lateral portions of the upper and lower pre-tarsal orbicularis oculi seems to yield the best results [57]. BoNT can also be used effectively to correct frowning (the procerus sign) when may be a form of upper facial dystonia, particularly common in patients with PSP [58, 59]. In a cross-sectional study, 114 blepharospasm patients who received ≥2 cycles of BoNT serotype A [onabotulinumtoxinA (n = 78), incobotulinumtoxinA (n = 35), or abobotulinumtoxinA (n = 1)] were interviewed immediately before re-injection to evaluate treatment satisfaction, time course of treatment effects, preferred injection intervals, Jankovic Rating Scale (JRS), and Blepharospasm Disability Index (BSDI) [60]. The most frequent injection interval was 12 weeks (46.5% subjects); 30.7% had an interval >12 weeks. 36.6% reported that treatment effects usually declined within 8 weeks; 69.6% within 10 weeks with BSDI scores indicating re-emergence of symptoms before re-injection. Overall, treatment satisfaction was high, but declined at the end of the cycle. Fifty-two percent of the subjects preferred an injection interval of <12 weeks. Although the standard-of-case 12-week interval is commonly used, in some patients flexible, individualized treatment interval may improve treatment satisfaction.

Botulinum toxin therapy is effective in secondary as well as primary blepharospasm, and toxin therapy can improve the quality of life [61, 62]. According to the 2016 AAN evidence-based review of the currently available clinical data available, it was concluded that onabotulinumtoxinA (based on two class II studies) and incobotulinumtoxinA (based on one Class I study) are probably effective in the treatment of blepharospasm (level B recommendation) and abobotulinumtoxinA (based on one Class II study) is possibly effective (level C recommendation). There are no quality studies to confirm the efficacy of rimabotulinumtoxinB (level U recommendation) [10]. The likely reason for the lack of optimal evidence supporting BoNT use in blepharospasm is robust benefits noted with BoNT in the initial open-label studies and the lack of alternate therapies which discouraged newer controlled clinical trials.

In a study comparing onabotulinumtoxinA and abobotulinumtoxinA in 212 patients with blepharospasm, duration of benefits was found to be similar in both groups. AbobotulinumtoxinA arm had higher rate of side effects like ptosis, dry eyes, tearing, blurred vision, double vision, hematoma, and foreign body sensation [63], which were attributed to higher diffusing properties of this toxin. However, Sampaio et al. found no difference between onabotulinumtoxinA and abobotulinumtoxinA with regard to duration of effect or adverse events in a single-blind, randomized comparison [64]. IncobotulinumtoxinA was found to be non-inferior to onabotulinumtoxinA, when compared in 300 patients with blepharospasm in a randomized, double-blind study [65]. There have been studies comparing onabotulinumtoxinA with other formulations such as Prosigne® (not available in the US) [66] and Meditoxin® (not available in the US) [67], and no significant difference was found between the groups. According to the 2016 AAN evidence-based review, incobotulinumtoxinA and onabotulinumtoxinA are equivalent in efficacy for treating blepharospasm based on two Class I effectiveness studies and one Class II study. AbobotulinumtoxinA and onabotulinumtoxinA are possibly equivalent for treating blepharospasm based on one class II study [10].

Oromandibular Dystonia and Bruxism

Oromandibular dystonia (OMD) in a patient with co-existent parkinsonism often suggests the possibility of MSA or some other atypical form of parkinsonism, but it can also be levodopa-induced in patients with PD. OMD is characterized by involuntary repetitive spasms mainly involving masticatory muscles but often includes lingual and pharyngeal muscles [68, 69]. OMD can be jaw-closing, jaw-opening, lateral jaw deviation, or a combination of these abnormal movements as well as bruxism (jaw clenching and teeth grinding) [70]. It can involve lips and tongue (mostly protrusion). Bruxism can occur while the patient is awake or asleep (nocturnal bruxism). If untreated, this can lead to tooth destruction, temporomandibular joint (TMJ) dysfunction, headaches, and disruption of the bed partner's sleep due to grinding sounds.

Supportive therapy includes the use of night guards and dental appliances. BoNT has been used to treat OMD and is most effective in treating jaw-closing and jaw-deviation dystonia [71]. There is limited literature related to the use of BoNT in the management of bruxism [72]. There are only two randomized controlled trials looking at the effectiveness of BoNT in bruxism [73, 74]. Injections are typically given in masseters and temporalis for jaw closing dystonia. Both the studies revealed a reduction in bruxism with BoNT; however, these studies had the small sample size and relied on questionnaires and portable EMG to establish the diagnosis of bruxism. According to a placebo-controlled, parallel design, polysomnogram study, onabotulinumtoxinA injected into masseter and temporalis improved sleep bruxism as demonstrated by significant improvement in clinical global impression ($p < 0.05$) and visual analogue scales ($p < 0.05$) [75].

For jaw-opening OMD, the most important muscle to be targeted with BoNT is the external pterygoid. Digastric and myohyoid muscles are also involved in some cases of jaw-opening dystonia and the submental muscle complex is often injected in our center in patients with jaw-opening dystonia with or without anterocollis and with or without associated parkinsonism. This form of jaw-opening dystonia, also referred to as "hyoid muscle dystonia," may benefit from BoNT injections into the appropriate muscles in about 71% of cases [76]. For jaw deviation, ipsilateral masseter or contralateral external pterygoid muscles may need to be injected to bring the jaw back to normal alignment. When there is associated jaw protrusion, both external pterygoids may be involved and may require injection [77]. The pterygoid muscle injections may have to be performed with EMG guidance, as these muscles are not easy to palpate.

Treatment of OMD with BoNT can improve speech and chewing [78]. An open-label study evaluated onabotulinumtoxinA for OMD in 62 patients and 73% of the subjects had a favorable response based on a global rating scale. In 115 patients with OMD, 42 (37%) visits were followed by some complications, primarily consisting of dysphagia [79]. In another study, 162 patients with OMD (more than half with jaw-closing dystonia) were injected with BoNT serotype A in masseters and submental muscle complex, or both with a mean follow-up of 4.4 ± 3.8 years. On a scale of 0–4 (4 = complete resolution), the mean global effect of BoNT was 3.1 ± 1.0, with the best response in jaw-closing dystonia. Complications such as dysphagia and dysarthria were reported in 11.1% of all treatment visits [70]. In another study, 18 patients with severe bruxism injected with onabotulinumtoxinA in bilateral masseter with the mean dose of 61.7 ± 11.1 units during 123 treatment visits. On a scale of 0–4 where 4 equals total abolishment of grinding the mean peak effect was 3.4 ± 0.9, mean total duration of response was 19.1 ± 17.0 weeks and only one subject (5.6%) reported experiencing dysphagia [71]. Another open-label study explored genioglossus injections of onabotulinumtoxinA for lingual protrusion dystonia in nine patients, who received a mean dose of 13.3 units into each genioglossus muscle [80]. In this study, five patients (55.6%) had moderate or marked reduction in tongue protrusion. One patient developed severe dysphagia requiring placement of a percutaneous gastrostomy (PEG) tube. An observational prospective study investigated the impact of BoNT treatment on the quality of life

(QoL) in 30 patients with prominent lingual dystonia as measured by oromandibular dystonia questionnaire-25 (OMDQ-25) scores [81]. Genioglossus, lateral and medial pterygoids, anterior digastric, masseter, and temporalis muscles were injected with abotulinumtoxinA in 27 patients and onabotulinumtoxinA in three patients. After BoNT treatment, the total OMDQ-25 score reduced from mean of 46.8 at baseline to 38.2 at 4 weeks ($p = 0.004$) and 39.6 at 8 weeks ($p = 0.008$). OnabotulinumtoxinA and abobotulinumtoxinA have received level C rating (possibly effective) for use in OMD [11]. There are no published studies in which incobotulinumtoxinA or rimabotulinumtoxinB were used for the treatment of OMD or bruxism.

Limb Dystonia

Unlike dystonic writer's cramp, which is probably the most common form of focal dystonia associated with abnormal contraction of the muscles of the fingers, wrist and arm producing abnormal posture, often detected by mirror maneuvers [82], the parkinsonian writer's cramp is characterized by an isometric contraction of the hand muscles resulting in a tight grip on the pen and minor flexion of the arm [83]. The data on the use of BoNT in focal hand dystonia (idiopathic rather than PD-related) are based on one class 1 study [84] and one class 2 study [85] of abobotulinumtoxinA and two class 2 studies on onabotulinumtoxinA [86, 87]. The most common side effect reported was the focal weakness. In an evidence-based review of BoNT in the treatment of focal hand dystonia, both abobotulinumtoxinA and onabotulinumtoxinA were considered to be possibly effective (level B recommendation) [11]. There are no published studies using incobotulinumtoxinA or rimabotulinumtoxinB for focal hand dystonia.

In young onset PD, foot dystonia often present as exercise-induced toe cramping that can progress to inversion of the foot and disability. Striatal deformities of the foot with unilateral equinovarus dystonic posture of the foot and extension of the great toe can present in up to 40% of untreated patients with advanced PD. It can also be a form of wearing off dystonia, or less frequently peak dose dyskinesias, in patients on levodopa therapy. There is no class 1 study confirming the efficacy and safety of BoNT for the treatment of foot dystonia but BoNT is widely used off-label for this indication. In an open-label pilot study, onabotulinumtoxinA was used to treat off painful dystonia induced by levodopa in 30 patients with PD [88]. Tibialis posterior, tibialis anterior, gastrocnemius, flexor digitorum longus, and extensor hallucis longus were injected with a median dose 40 IU for each muscle, distributed in two sites. In all patients, the pain originating from afferent nerve fibers within the dystonic muscle, improved within 10 days and seven patients noted an improvement of foot posture on walking.

BoNT has also been found helpful in symptomatic relief of pain and in preventing skin damage in patients with "dystonic clenched fist," a relatively common condition in advanced stages of CBD and other parkinsonian disorders [89]. In one

small study, abobotulinumtoxinA was injected into dystonic clenched fist of three CBD patients [90]. Lumbricals, flexor pollicis brevis, flexor digitorum superficialis, and flexor carpi ulnaris muscles were injected. All three patients had significant improvement in pain and muscle relaxation after the first treatment without any functional improvement because of associated apraxia. There was an improvement in hand posture in one patient and gain in palmar hygiene in the other patient. In an observational study of 26 CBD patients, all 11 who received BoNT for their dystonic limb posturing had symptomatic benefits as reflected by improvement in the Unified Dystonia Rating Scale (UDRS) [91]. These studies suggest that BoNT injections for dystonia in CBD can be used to reduce pain, improve hygiene, prevent secondary contractures, and on occasion, improve limb function when applied early in the disease course [92, 178].

Cervical Dystonia

Cervical dystonia is the most common form of axial dystonia. When it is present in patients with PD or other parkinsonian disorders, it often manifests as neck flexion ("dropped head" or "bent spine") and may be accompanied by truncal flexion (camptocormia), scoliosis, pisa syndrome or tilting of the trunk to one side (also known as pleurothotonus) or a combination of these postures [4].

Cervical dystonia is characterized by involuntary patterned contractions of cervical musculature resulting in abnormal movements or postural changes of the head, neck, and shoulders [93, 94]. Cervical dystonia can lead to clinically heterogeneous directional presentations of the neck, such as torticollis, laterocollis, retrocollis, or anterocollis. The patient may have associated shoulder elevation, head oscillation, neck pain, and a variety of alleviating maneuvers, also referred to as sensory tricks [95].

Anterocollis is more typically associated with parkinsonism, specifically PD and MSA [7] whereas neck extension is more typically present in PSP [47]. The neck extension in PSP may be a form of axial rigidity rather than dystonia [47]. Various theories have been proposed for anterocollis including neck extensor myopathy, imbalanced rigidity of anterior and posterior neck muscles, as well as dystonia [182, 96].

BoNT is considered the most effective treatment for cervical dystonia. According to the American Academy of Neurology Practice Guideline report, abobotulinumtoxinA and rimabotulinumtoxinB have level A evidence, whereas onabotulinumtoxinA and incobotulinumtoxinA have level B evidence for the treatment of cervical dystonia [10]. The reason for lack of evidence to support efficacy and safety of BoNT in the treatment of neck flexion (anterocollis), the most common abnormal neck posture in parkinsonism, is because these patients are excluded from cervical dystonia studies of BoNT due to the belief that anterocollis is difficult to treat with BoNT and bilateral injections of sternocleidomastoid and scalene muscles is associated with dysphagia. However, at our center we have successfully treated some of these patients with anterocollis using BoNT, with minimal or no side adverse effects

[7]. Avoiding the lower portions of sternocleidomastoid muscle can also lower the risk of dysphagia. There are case reports of the use of injections of BoNT in the lower third of the sternocleidomastoid in patients with refractory anterocollis with marked benefit and no complications [97]. Deep prevertebral muscles such as longus colli and longus capitis may also be involved in anterocollis, but these are difficult to reach although the injury to vertebral vessels and other complications may be avoided by use of imaging techniques [98, 99]. Sometimes injections into submental muscle complex may be helpful when anterocollis is accompanied by downward jaw deviation due to contractions of the hyoid muscles [7]. Some have categorized anterocollis into conceptual anterocollis, anterocaput, and forward sagittal shift, and have suggested that electromyography, computed tomography, magnetic resonance imaging, FDG-positron emission tomography, endoscopy, and other techniques may need to be utilized to achieve optimal results with BoNT treatment [100]. Retrocollis is relatively easy to treat by injections into posterior neck muscles such as splenius capitis or splenius cervicis [101].

Levodopa-Induced Dyskinesias

Levodopa-induced dyskinesia (LID) is categorized as "peak-dose dyskinesias," "diphasic dyskinesia," and "off-period dystonia" based on the relationship to levodopa dosing. Off-period dyskinesia, typically in a form of dystonia, often responds to adjustments in dopaminergic drugs, addition of catechol-O-methyltransferase (COMT) inhibitor, monoamine oxidase B (MAO-B) inhibitors, dopamine agonists, baclofen, subcutaneous apomorphine, or BoNT [102]. Off-period dystonia accounts for about 30% of the levodopa-induced dyskinesias. Levodopa-related dystonia typically presents when levels of levodopa are rising or falling, but in most cases levodopa-related dystonia is a wearing-off phenomenon. It may be seen in the morning before the first dose of medication or in-between doses. It typically manifests as painful muscle spasms, toe curling, foot flexion, and inversion. Off-period dystonia occurs when the striatal dopamine concentration is low [103, 104]. Both presynaptic dopamine depletion and postsynaptic mechanisms play an important role in LID [103, 105]. Some groups propose that intermittent dosing of levodopa is more likely to shorten the response to each dose of levodopa as compared to a continuous administration [106, 183]. In some cases, BoNT may alleviate prolonged painful foot dystonia. In one study, eight levodopa-treated PD patients with frequent and bothersome cervical-predominant LID, regardless of any antidyskinetic treatment were randomized to receive EMG-guided onabotulinumtoxinA or placebo with normal saline [107]. Assessments occurred at 0, 1, 3 (crossover visit), 4, and 6 months after enrollment, with blinded injections administered at the 0- and 3-month visits. Primary outcome measure was a change in the Goetz dyskinesia rating scale (GDRS, 0–4, higher is worse), modified for the cervical region, 1 month after each injection (1- and 4-month study visits). Only four patients completed the 6-month study before voluntarily stopping due to excessive neck

weakness. OnabotulinumtoxinA improved GDRS scores for the resting but not action-induced dyskinesias. Only one subject requested onabotulinumtoxinA injections for ongoing post-study management of his LID.

Myoclonus and Myorhythmia

BoNT may be helpful in the treatment of limb myoclonus associated with CBD or other parkinsonian disorder. Although no well-controlled trials have been conducted, this treatment, however, has been reported to be effective in the treatment of segmental myoclonus [29, 108].

Myorhythmia is described as a repetitive, rhythmic, jerky movement of slow (1–4 Hz) frequency, affecting mainly cranial and limb muscles, usually at rest but sometimes noted also with sustained posture [109]. It may be associated with parkinsonian signs such as rigidity and bradykinesia. BoNT may be safe and effective in the treatment of limb myorhythmia.

Camptocormia

Skeletal and joint deformities, such as striatal hand and feet, bent spine, camptocormia, and pisa syndrome, are common and often under-recognized features of PD and atypical parkinsonism [48, 110–112]. Although usually caused by axial dystonia, there are many pathophysiologic mechanisms of camptocormia, characterized by marked flexion (usually more than 45°) of thoracolumbar spine [23, 96, 113]. Walking typically exacerbates dystonic camptocormia and maneuvers such as "climbing the wall" and supine position tends to relieve the condition. The prevalence of camptocormia in PD has been reported between 4.1% and 17.6% [114]. Conventional anti-PD and anti-spasticity medications are not very beneficial in the treatment of camptocormia. Hence, BoNT and other strategies like DBS may have to be considered in these patients [115]. In one study, 9 of the 11 patients with camptocormia received onabotulinumtoxinA injections into the rectus abdominus with notable improvement in 4 of the 9 patients [116]. These patients had clinical evidence of contraction of rectus abdominus and received injections of between onabotulinumtoxinA 300 and 600 units per treatment visit. The effect lasted for about 3 months after each injection with a mean duration of maximal response in three patients of 10 ± 6 weeks. There have been few negative trials using BoNT serotype A including onabotulinumtoxinA, abobotulinumtoxinA and incobotulinumtoxinA, with injections into only iliopsoas muscle or both iliopsoas and rectus abdominus muscles, using either blind injection technique, ultrasound or CT guidance [117, 139, 179]. Overall, the efficacy of BoNT for camptocormia is controversial, but when the most involved muscles are selected for injection with appropriate dose and skilled technique, the results can be quite satisfactory.

Sialorrhea

Sialorrhea, present in approximately 75% of the patients, is a common source of embarrassment and social handicap, skin irritation around the mouth, and swallowing problems that can lead to impaired quality of life of patients with PD [4].

In a study, where unstimulated saliva production was measured over 5 min revealed that patients with PD produce less saliva than normal controls [163]. Female PD patients produce less saliva than men with Parkinson's disease and levodopa therapy increases the salivary flow in these patients [177]. This suggests that the cause of sialorrhea in PD is due to impaired reflex deglutition rather than hypersecretion. Even in PD patients with no dysphagia complaints, the oral and pharyngeal parts of the swallow are significantly slower; they required more swallows to clear a small amount of liquid and have fewer swallows followed by expiration [162]. The possible causes of impaired deglutition include involvement of motor nucleus of the vagus, degeneration of the myenteric plexus in the esophagus, and flexed posture. In addition, dysregulation of the salivary function due to the involvement of salivary parasympathetic ganglia has also been postulated.

The treatment options for sialorrhea in PD include anticholinergic drugs like oral glycopyrrolate, sublingual ipratropium bromide spray, sublingual atropine drops, clonidine, and modafinil [133]. Side effects of anticholinergic drugs preclude their use, especially in the elderly. BoNT serotype A has been shown to be effective for sialorrhea [147, 149, 151]. In various studies using onabotulinumtoxinA for sialorrhea, the dose ranged from 5 to 50 and 5 units per parotid and submandibular gland, respectively and it significantly reduced drooling in PD, MSA, and DLB patients for approximately 4 months [173]. The typical dose for abobotulinumtoxinA for sialorrhea in three published studies ranged from 75 to 146.2 units and 78.7 units per parotid and submandibular gland, respectively. BoNT type B injections into the parotid and submandibular glands also appear to be effective in the treatment of PD-related sialorrhea and may have a potential advantage over BoNT type A [132, 158]. BoNT serotype B leads to greater incidence of dry mouth when used in the treatment of cervical dystonia and hence may be considered the treatment of choice for sialorrhea [175, 176]. Ultrasound guidance may be helpful in improving the accuracy of injection into the parotid gland [137]. According to the evidence-based review, rimabotulinumtoxinB, abobotulinumtoxinA, and onabotulinumtoxinA all have level B recommendation for sialorrhea. There are insufficient data on the use of incobotulinumtoxinA (level U) for sialorrhea [9]. The facial nerve is close to parotid gland and caution must be taken when injecting for sialorrhea. The optimal number of injections into the parotid gland is debatable; some institutions distribute the dose within two injection sites but other may choose to give up to nine injections distributed in a grid-like pattern [148].

Hyperhidrosis

Sweating disorder, either hypohidrosis or in particular hyperhidrosis were reported by 64% of PD patients and by 12.5% of controls ($p < 0.005$) [174]. Sweating problems, such as "drenching sweats," predominantly happen in off periods and in on periods with dyskinesia. It is suggestive of evidence of dysautonomia and usually does not correlate with severity of the disease. Patients with PD have less sweating in the palms and therefore axial hyperhidrosis could be a compensatory phenomenon for reduced sympathetic function in the extremities in PD patient [169].

There are no studies specifically examining the use of BoNT in sweating disorders in PD patient [7, 23] but this treatment has been found effective in the treatment of essential hyperhidrosis, which is defined as excessive sweating of the palms, feet or axillae [155]. Previous studies have shown the efficacy of intradermal injections of BoNT for focal hyperhidrosis [156, 172]. According to the evidence-based review by Therapeutic and Technology Assessment Subcommittee of the American Academy of Neurology, BoNT has level A evidence for use in axillary hyperhidrosis [9, 157].

Achalasia

Different reasons for swallowing problems in PD patients include proximal dysphagia due to impaired deglutition or flexed neck posture, and achalasia. In Parkinson's patients, reduced pharyngeal constriction and delay in airway closure relative to the arrival of the bolus at the cricopharyngeal (CP) sphincter are the most common abnormalities causing proximal dysphagia [138]. Other studies have suggested hyoid displacement, CP sphincter opening, vocal fold adduction, epiglottic movements, palatal elevation, laryngeal excursions, and prolonged pharyngeal transit time as other reasons for the proximal dysphagia. This can result in the vallecular and pyriform residue, laryngeal penetration, and aspiration.

Several studies have provided evidence for the safe and effective use of BoNT type A for dysfunction of the CP muscle [119, 121, 128, 153]. Injections in the dorsomedial part and on both sides into the ventrolateral part of the CP with doses between 80 and 120 units of abobotulinumtoxinA have been described [170]. Haapaniemi et al. reported good results with the use of onabotulinumtoxinA in posterolateral part of the CP in patients with proximal dysphagia [142].

Achalasia results in aperistalsis and impaired relaxation of the lower esophageal sphincter (LES). Pathophysiologically, achalasia seems to be due to loss of inhibitory neurons within the esophageal myenteric plexus that uses nitric oxide and vasoactive intestinal polypeptides as neurotransmitters [161]. Lewy bodies have been documented in myenteric plexus in PD patient's with achalasia, primarily in the inhibitory vasoactive polypeptide neurons [118]. Also, loss of neurons in the dorsal

motor nucleus of the vagus has been described [145]. The treatment of achalasia is directed at reducing the gradient across the lower esophageal sphincter (LES). Laproscopic myotomy and pneumatic dilatation are the most commonly used treatments with comparable clinical efficacy. LES pressure can be transiently reduced by smooth muscle relaxants like BoNT [143, 164]. BoNT presumably counteracts the unopposed LES stimulation by cholinergic neurons, helping to restore the LES to a lower resting pressure by approximately 50% [143, 153]. The total dose of 100 units of onabotulinumtoxinA may need to be endoscopically injected into the LES in multiple aliquots in a ring around the sphincter, increasing the dose to 200 units has been recommended in some studies [123]. OnabotulinumtoxinA markedly improved symptoms in 75% of achalasia patients, but 50% of patients relapsed within 6 months. Patients above age 60 and those with higher esophageal contractility (pressure waves usually >40 mmHg in the esophageal body) tend to have sustained response, sometimes up to 1.5–2 years after a single onabotulinumtoxinA injection [159].

Seborrhea

Seborrhea is a common dermatological disorder associated with PD. Previous studies have shown that parkinsonian male patients show a higher sebum excretion than parkinsonian females and healthy subjects in all the skin locations, with particular significance on the forehead. Different theories for seborrhea have been proposed including increased sebum excretion rate due to hyperactivity of the parasympathetic system, possible action of androgens, excess melanocyte-stimulating hormone secretion because of PD-related dopamine depletion, and high malassezia yeast density on the skin of patients with PD [126, 152]. BoNT injections into the affected skin area may be helpful [7, 171], as it has been found effective in acne, another hypercholinergic dermatologic condition [136, 184]. It has been proposed that BoNT inhibits comedogenesis by interrupting cholinergic transmission between autonomic nerve terminals and secretary glands or by yet unknown anti-inflammatory effects.

Overactive Bladder

Urinary problems may present as urinary frequency and urgency, nocturia and incontinence in patients with PD [181]. Even though these symptoms occur as a consequence of aging detrusor hyperreflexia, which is frequently responsible for these symptoms, it is a relatively common urological problem in the PD population and ranges from 38% to 71% [167]. Detrusor hyperreflexia is presumably a result of the loss of normal inhibition by the basal ganglia and frontal cortex on the sacral spinal cord bladder contractions as a result of which the bladder capacity is much

smaller in patients with PD [125, 127]. Urinary retention with or without neurogenic incontinence in parkinsonian patient suggests a diagnosis of MSA [6]. In these patients, EMG reveals signs of denervation in Onuf's nucleus in the sacral spinal cord; this is not seen in PD.

Even though anticholinergic agents, often considered as first-line treatment for overactive bladder, presumably act through "peripheral" mechanisms they often cause cognitive and other central anticholinergic adverse effects, particularly in the elderly [154]. These antimuscarinic drugs include oxybutynin, tolterodine, solifenacin, and darifenacin. Mirabegron, a new beta 3 adrenoreceptor agonist, promotes relaxation of the detrusor smooth muscle and improves urine storage, presumably with fewer side effects [131]. Alpha adrenergic agonists such as alfuzosin, doxazosin, prazosin, terazosin, and tamsulosin do not have a high level of evidence for controlling overactive bladder [122].

BoNT injections into the bladder wall is an effective strategy to increase bladder capacity, and improving urge and incontinence in patients with overactive bladder associated with neurogenic and idiopathic detrusor overactivity [124, 168]. One and 3 months after injection of 200 units botulinum toxin type A into the detrusor muscle, all six patients with parkinsonism (four patients with PD and two with MSA) reported marked reduction in the urinary frequency with no systemic side effects [141]. In another study, 16 PD patients received 500 units of intradetrusor injections of abobotulinumtoxinA and the mean functional bladder capacity increased from 198.6 ± 33.7 to 319 ± 41.1 ml [146]. Similar results have been reproduced in other studies [140, 160].

Based on the result of two class 1 studies of BoNT in neurogenic detrusor overactivity, the Therapeutic and Technology Assessment Subcommittee of the American Academy of Neurology concluded that there is level A evidence for the recommendation that BoNT should be offered as a treatment option for this urinary disorder [9]. In addition to treating detrusor hyperactivity, BoNT has demonstrated promising results for other lower urinary tract symptoms such as voiding dysfunction due to benign prostatic hypertrophy [134].

Constipation

Anismus due to excessive contractions of the muscles of the rectum has been proposed as a mechanism for constipation as a result of functional obstruction at the pelvic outlet by paradoxical contraction of the striated sphincter muscles while straining during defecation [185]. Excessive straining is present in up to 83% of PD patients [135, 165]. Central defecation centers in the lumbosacral spinal cord and sacral parasympathetic nuclei, including Onuf's nuclei control the propulsive actions of the distal colon and defecation [150, 186]. Deposition of Lewy bodies and synuclein pathology in the caudal spinal cord is the most likely substrate for the slow-transit time and dyssynergic defecation observed in the majority of PD patients [129]. Prolonged colon transit time is in part attributed to paradoxical contraction of

the puborectalis and external anal sphincter during straining [180, 185]. BoNT injections have been shown to be helpful in the treatment of patients affected by outlet-obstruction constipation and defecatory dysfunction due to pelvic floor dyssynergia [130, 166]. In one study, 10 of the 18 PD patients with outlet constipation, treated with 100 units of type A botulinum toxin, injected into two sites on either side of the puborectalis muscle under ultrasound guidance, reported symptomatic improvement at 2 months evaluation [130]. Anorectal tone, measured by a manometry during straining decreased from 96.2 ± 17.1 to 45.9 ± 16.2 mmHg at 1 month evaluation, and to 56.1 ± 10.7 mmHg at 2 months. Another study involving 10 PD patients with outlet-type constipation injected with BoNT in the puborectalis muscle, showed reduced anorectal tone during straining [120]. There is a need for further and larger double-blind, placebo-controlled studies to establish the safety and efficacy of BoNT in the treatment of constipation in patients with PD [23].

Conclusion

Parkinson's disease (PD) and other parkinsonian syndromes are chronic, progressive neurodegenerative diseases with the multitude of the motor and non-motor symptoms. BoNT is the useful treatment modality for the management of many of these symptoms and can make a significant impact on the quality of life of these patients. It has proven to be a safe and effective therapy for the management of blepharospasm and lid apraxia, cervical dystonia (anterocollis), focal hand dystonia, bruxism, hyperhidrosis, and detrusor overactivity. It is also helpful in the management of foot dystonia, camptocormia, PD-related tremor, constipation, seborrhea, and achalasia. While many conditions are not approved indications, botulinum toxin may be considered in some of these patients with disabling symptoms, unresponsive to other conventional therapies.

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